

There is written description support in the specification regarding the contaminating levels of adenoviral helper virus in a recombinant AAV preparation after four round of cesium chloride centrifugation. See the specification at page 35, lines 1-5 which describes that the rAAV preparation is purified from contaminating adenovirus helper and describes a method of detecting the amount of contaminating adenovirus in a rAAV preparation. In addition, other methods for detecting contaminating adenovirus helper were known by those of skill in the art as of the priority date of this application. The specification provides sufficient written description to inform a skilled artisan that Applicants were in possession of the claimed invention as a whole at the time the application was filed. Therefore, the claims are in compliance with Section 112, first paragraph written description requirements.

Reconsideration and withdrawal of this rejection is requested.

- II. Claims 19-24, 26-28 and 30-35 are rejected under 35 USC 112, first paragraph, because the specification is not enabling for any and all rAAV vectors wherein the ApoE encoding sequences are not linked to a promoter or wherein multiple ITRs or multiple ApoE encoding sequences are present, or wherein the contaminating levels of adenoviral helper virus are lower than the levels of contaminating adenoviral helper virus after subjecting the rAAV to four rounds of CsCl centrifugation or wherein the vector is administered by any method for the reasons of record set forth in the previous office action of 11-23-01 and 7-22-02.

Applicants respectfully traverse this rejection.

The claims recite that the rAAV comprises a 5' AAV ITR, nucleic acid encoding human ApoE operably linked to regulatory sequences which direct its expression, and a 3' AAV ITR. The Examiner alleges at page 3 of the Office Action that the specification does not reasonably provide enablement for any and all rAAV vectors wherein the ApoE encoding sequences are not linked to a promoter. The pending claims recite that the nucleic acid encoding human ApoE is operably linked to regulatory sequences that direct its expression.

The examiner admits the application is enabling for a composition comprising a recombinant adeno-associated virus (rAAV suspended in a biological compatible carrier), wherein the rAAV comprising (i) a 5' AAV ITR, (ii) a nucleic acid sequence encoding human ApoE operably linked to a eukaryotic promoter, and (iii) a 3' AAV ITR, and wherein the level of contaminating adenoviral helper virus is the same as that obtained by subjecting said recombinant AAV to four rounds of cesium chloride centrifugation.

The examiner also admits that the application is enabling for a method of delivering ApoE to a mammal with atherosclerosis, wherein said method comprises the step of administering to the mammal intramuscularly the composition comprising the rAAV and wherein the ApoE encoding sequence in the composition is expressed in the mammal and wherein a cytotoxic immune response directed against rAAV-transduced cells of the mammal expressing ApoE is absent in the mammal.

It is the level of purity of the composition comprising the rAAV from adenovirus helper virus that permits the rAAV to avoid a destructive immune response, such as, inflammation or extensive tissue damage. See specification at page 40, lines 18-23.

Applicants request reconsideration and withdrawal of the outstanding rejection.

III. Claims 19-24, 26-28 and 30-35 have been rejected under 35 USC 112, second paragraph, as being indefinite for the reasons set forth in the office action of 11-23-01. The examiner states that the specification does not disclose what would be considered the contaminating levels of adenoviral helper virus in the recite recombinant AAV composition that is purified by four rounds of cesium chloride gradient centrifugation, and therefore, the metes and bounds of the claimed invention is not clear.

Applicants respectfully traverse this rejection.

The specification teaches how to purify rAAV by performing four rounds of cesium chloride gradient centrifugation. The invention further describes a method of detecting the amount of contaminating adenovirus in a rAAV preparation.

See, page 35, lines 1-5. In addition, the present specification teaches that the rAAV is sufficiently pure of helper adenovirus to avoid a destructive immune response.

Applicants request reconsideration of the rejection.

- IV. Claims 19-24, 26-28 and 30-35 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-4 of US Patent 5,866,522. Claims 19-24, 26-35, and 36-38 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 7-11 of co-pending Application No. 09/757,673. Claims 19-24, 26-35, and 36-38 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting over claims 1-6, 9, 20, 21, 23, 25, 26 and 27 of co-pending Application No. 09/237,064.

Applicants request that the double patenting and provisional double patenting rejections be deferred until the claims are in condition for allowance.

- V. Claims 19-24, 26-28 and 30-38 are rejected under 35 USC 103(a) as being unpatentable over Podsakoff et al, US 5,858,351, in view of Kaplitt et al, US 6,503,888, Gage and Ueba, US 6,236,484, Wilson, Fisher, and Gao, US 6,270,996 or Wilson, Fisher and Gao, US 5,756,283 and Kashyap (item CV).

The examiner notes that the inventors of the Wilson '996 and Wilson '283 patents differ from those of the present invention. However, Applicants note that the cited patents and the present application were owned by the same entity at the time the inventions were made.

The examiner admits Podsakoff does not teach an rAAV vector composition comprising 5' ITR, nucleic acid sequence encoding ApoE, and 3' ITR, wherein the level of contaminating Ad helper virus is no greater than that obtained by subjecting said recombinant rAAV to four rounds of CsCl centrifugation. The examiner relies on secondary references Kaplitt, Gage and Ueba, and Wilson, to support the position that it was routine in the art to characterize an AAV preparation by histochemical staining of cells and purify the virus by multiple rounds of purification. The examiner points particularly to column 8, lines 60-64 and column 20, lines 37-40 of Kaplitt. Kashyap is relied upon for teaching that genetic dyslipoproteinemias are ideal candidates for gene therapy and teach an ApoE adenoviral vector.

Applicants respectfully traverse this rejection.

Applicants are the first to note that typical preparations of rAAV produced with helper virus, and particularly Ad helper virus, when injected intramuscularly, induced a destructive immune response.

No combination of the cited documents recognizes the presence of the destructive immune response in an rAAV preparation contaminated by helper virus, much less provides a solution which avoids such a destructive immune response.

Kaplitt describes the use of an AAV-derived virus for delivery of exogenous DNA for treatment of nervous system disorders. Kaplitt describes production of such a virus using a helper adenovirus which may be removed by heat inactivation at 56 °C for 30 minutes, or separated by centrifugation in a cesium chloride gradient.

Kaplitt neither teaches nor suggests the use of four rounds of cesium chloride gradient centrifugation. Nor does Kaplitt recognize the immune response which can be induced by helper virus (even if inactive) which is present as a contaminant in an composition, and in particular, a composition adapted for intramuscular delivery.

Further, by use of heat inactivation in its examples, Kaplitt makes it clear that the only thing his preparations are “free” of, is the lytic activity of adenovirus and its ability to infect cells. The adenoviruses are still present in the preparation, and thus, still capable of inducing an immune response.

It is recalled that a CPA of this application was filed September 13, 2001. Wilson ('996) and Wilson ('283), would qualify as prior art only under subsection 102(e), as they issued after the effective date of this application. However, these two patents are not available as prior art under Section 103(c), because the subject matter and the claimed invention were, at the time the invention was made, subject to an obligation of assignment to the same person.

Gage and Ueba ('484 patent) has an effective 102(e) date of May 14, 1998, nearly two years after applicants' effective priority date. Accordingly, Applicants disagree that this document is useful as prior art, or to show the state of the art in 1996.

As previously noted, Podsakoff does not suggest the use of ApoE and Kashyap does not suggest the delivery of ApoE via a rAAV vector. Further, the combined documents fail to recognize the level of purity from helper adenovirus necessary for an rAAV to obtain the results provided by the present invention.

Further, the present invention provides compositions which are 2 logs more pure of contaminating wild-type (wt) AAV than Podsakoff. Note, when purified as described in the present invention, rAAV preparations contain <1 infectious unit wt AAV per 10^9 genomes rAAV. See, page 35, lines 5-6 of the specification. In contrast, Podsakoff detects wt AAV contamination of approximately 1 in 10^7 . See, col. 19, lines 16-17 of the '351 patent.

Thus, the rAAV of the present invention are more pure than taught by Podsakoff. Again, it is noted that Kashyap fails to suggest anything about the use of rAAV vectors. Thus, the combination is deficient.

In addition, none of the cited documents recognizes that the mere presence of contaminating adenoviruses (even in the absence of the ability to express adenoviral proteins) may cause a destructive immune response. It is only the inventors who have recognized the significance of eliminating adenoviral contamination *and not just contamination by adenoviral function* which led to the present invention.

The cited combination fails to provide both the motivation to combine the cited references in a manner which suggest the invention, and a reasonable expectation of success. Absent recognition of the immune problems found upon delivery of rAAV, and particularly intramuscular delivery of rAAV, caused by contamination with helper virus, there is no teaching or suggestion of the invention.

Applicants request reconsideration of the present invention.

Other Issues:

Applicants submitted an electronic Information Disclosure Statement on February 21, 2003, prior to issuance of the present Office Action. Applicants request consideration of US Patent 6,506,379, which was listed in that IDS at this time.

The Director of the U. S. Patent and Trademark Office is hereby authorized to charge any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees paid on the filing, or during prosecution of this application to Deposit Account No. 08-3040.

Respectfully submitted,

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